21: Trends Endocrinol Metab 1999 Aug;10(6):216-222 Related Articles

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TGF-beta Family Members and Gonadal Development.

Josso N, di Clemente N.

Unite de Recherches sur l'Endocrinologie du Developpement (INSERM), E Superieure, Departement de Biologie, 1 rue Maurice-Arnoux, 92120 Montr

Several members of the transforming growth factor beta (TGF-beta) family in gonadal development; namely, TGF-beta itself, inhibins, activins, anti-M hormone (AMH) and GDF-9. These proteins do not affect initial gonadal or but play either a stimulatory or inhibitory role in the division and differentia gonadal cells and in meiotic maturation in the female. Furthermore, as shov transgenic mouse technology, both AMH and inhibin act as tumor suppress

PMID: 10407395 [PubMed - as supplied by publisher]

22: Cell Tissue Res 1999 Jul;297(1):103-10 Related Articles

Cell & Tissue Research

Expression of a novel member of the TGF-beta superfamily, growth/differentiation factor-15/macrophage-inhibiting cytoki 15/MIC-1) in adult rat tissues.

Bottner M, Suter-Crazzolara C, Schober A, Unsicker K.

Department of Neuroanatomy, University of Heidelberg, Im Neuenheimer I 69120 Heidelberg, Germany.

We have cloned a novel member of the transforming growth factor-beta (T superfamily from a human placental cDNA library. The sequence is identic recently published sequences, of which only one (macrophage inhibitory cy MIC-1) has been characterized in terms of function. In light of the present c

demonstrating the wide distribution of the mRNA and putative multifunctic propose to name this molecule growth/differentiation factor-15/MIC-1 (GD The deduced amino acid sequence reveals typical features of a secreted mol epithelium of the choroid plexus is the only site in the adult brain expressin levels of GDF-15/MIC-1 mRNA. Many epithelia of non-neural tissues incl the prostate and intestinal mucosa, bronchi and bronchioli, secretory tubuli submandibular gland, and lactating mammary gland are prominent sites of 1 synthesis. GDF-15/MIC-1 is also strongly expressed by macrophages in tl gland. Thus, GDF-15/MIC-1, like many other members of the TGF-beta su widely distributed in adult tissues, being most strongly expressed in epitheli macrophages.

PMID: 10398887 [PubMed - indexed for MEDLINE]

☐ **23:** Mol Endocrinol 1999 Jun;13(6):1035-48 Related Articles

Paracrine actions of growth differentiation factor-9 in the man ovary.

Elvin JA, Clark AT, Wang P, Wolfman NM, Matzuk MM.

Department of Pathology, Baylor College of Medicine, Houston, Texas 770

Although the transforming growth factor-beta (TGF-beta) superfamily is th family of secreted growth factors, surprisingly few downstream target gene signaling pathways have been identified. Likewise, the identities of oocyte- secreted factors, which regulate important oocyte-somatic cell interactions, largely unknown. For example, oocytes are known to secrete paracrine grov which are necessary for cumulus expansion, induction of hyaluronic acid sy suppression of LH receptor (LHR) mRNA synthesis. Our previous studies c that absence of the TGF-beta family member, growth differentiation factor- blocks ovarian folliculogenesis at the primary follicle stage leading to infert present study, we demonstrate that mouse GDF-9 protein is expressed in all beginning at the type 3a follicle stage including antral follicles. To explore functions of GDF-9 in the later stages of folliculogenesis and cumulus expa produced mature, glycosylated, recombinant mouse GDF-9 using a Chinese ovary cell expression system. A granulosa cell culture system was establish determine the role of GDF-9 in the regulation of several key ovarian gene p semiquantitative RT-PCR. We find that recombinant GDF-9 induces hyalu synthase 2 (HAS2), cyclooxygenase 2 (COX-2), and steroidogenic acute re protein (StAR) mRNA synthesis but suppresses urokinase plasminogen acti and LHR mRNA synthesis. Consistent with the induction of StAR mRNA b recombinant GDF-9 increases granulosa cell progesterone synthesis in the a FSH. Since induction of HAS2 and suppression of the protease uPA in cum key events in the production of the hyaluronic acid-rich extracellular matrix produced during cumulus expansion, we determined whether GDF-9 could process. Using oocytectomized cumulus cell-oocyte complexes, we show th

recombinant GDF-9 induces cumulus expansion in vitro. These studies den GDF-9 can bind to receptors on granulosa cells to regulate the expression o gene products. Thus, in addition to playing a critical function as a growth a differentiation factor during early folliculogenesis, GDF-9 functions as an o secreted paracrine factor to regulate several key granulosa cell enzymes inv cumulus expansion and maintenance of an optimal oocyte microenvironme which are essential for normal ovulation, fertilization, and female reproduc

PMID: 10379900 [PubMed - indexed for MEDLINE]

☐ **24:** J Neurosci Res 1999 Jun 1;56(5):482-92 Related Articles

InterScience

Localized expression of BMP and GDF mRNA in the rodent b

Soderstrom S, Ebendal T.

Department of Neuroscience, Biomedical Center, Uppsala University, Swe

Expression of BMP- and GDF-related factors within the transforming grow (TGF-beta) superfamily was examined in the rat and mouse brain by in situ hybridization. Strong signals were obtained in neurons for GDF-1 and GDF is expressed at postnatal day 6 in the cerebral cortex, hippocampal CA1 thr neurons, while only weakly expressed by cells in the dentate gyrus. Granule neurons in the polymorph layer of the dentate gyrus are GDF-1-positive, as majority of neurons in the cortex. GDF-10 shows a distinct pattern of expre strong labelling was seen in the superficial layers of cortex, notably in the p cingulate cortex, and in CA3 and dentate gyrus. From postnatal day 21, GD expression is strong in the hippocampus, cortex, and thalamic nuclei, while expression becomes restricted to the granule cell layer in the dentate gyrus. OP-1 expression is restricted throughout development to cells of the medial nucleus, choroid plexus, and leptomeninges. The markedly different expres of these BMPs suggest they serve separate functions in the brain.

PMID: 10369215 [PubMed - indexed for MEDLINE]

☐ **25:** J Cell Physiol 1999 Jul;180(1):1-9 Related Articles

InterScience

Myostatin, a transforming growth factor-beta superfamily me expressed in heart muscle and is upregulated in cardiomyocyte infarct.

Sharma M, Kambadur R, Matthews KG, Somers WG, Devlin GP, Con Fowke PJ, Bass JJ.

Growth Physiology, AgResearch, Ruakura, Hamilton, New Zealand.
SharmaM@agresearch.cri.nz

Myostatin is a secreted growth and differentiating factor (GDF-8) that belor transforming growth factor-beta (TGF-beta) superfamily. Targeted disruptic myostatin gene in mice and a mutation in the third exon of the myostatin ge muscled Belgian Blue cattle breed result in skeletal muscle hyperplasia. He myostatin has been shown to be involved in the regulation of skeletal muscl both mice and cattle. Previous published reports utilizing Northern hybridiz shown that myostatin expression was seen exclusively in skeletal muscle. A lower level of myostatin mRNA was also reported in adipose tissue. Using reverse transcription-polymerase chain reaction (RT-PCR) technique and W blotting with anti-myostatin antibodies, we show that myostatin mRNA and not restricted to skeletal muscle. We also show that myostatin expression is the muscle of both fetal and adult hearts. Sequence analysis reveals that the heart myostatin cDNA sequence contains an 11 nucleotide deletion in the th causes a frameshift that eliminates virtually all of the mature, active region Anti-myostatin immunostaining on heart sections also demonstrates that my protein is localized in Purkinje fibers and cardiomyocytes in heart tissue. Fu following myocardial infarction, myostatin expression is upregulated in the cardiomyocytes surrounding the infarct area. Given that myostatin is expres and adult hearts and that myostatin expression is upregulated in cardiomyoc infarction, myostatin could play an important role in cardiac development a physiology.

PMID: 10362012 [PubMed - indexed for MEDLINE]

☐ **26:** Biochem Biophys Res Commun 1999 Mar 16;256(2):419-24 Related Articles

Bone morphogenetic protein-3b (BMP-3b) gene expression is c with differentiation in rat calvarial osteoblasts.

Hino J, Matsuo H, Kangawa K.

National Cardiovascular Center Research Institute, Osaka, Fujishirodai, Sui Japan.

BMP-3b (also called GDF-10) is a novel BMP-3-related protein recently di: rat femur tissue. Gene expression of BMP-3b in osteoblastic cells and its re prolonged culture, BMP-2 and transforming growth factor beta1 (TGF-beta examined. The BMP-3b gene was highly expressed in rat osteoblasts obtain calvarial bones but not in the osteoblastic cell lines (MC3T3-E1 and U2-OS mRNA increased during osteoblastic differentiation in prolonged culture an associated with increased alkaline phosphatase (ALPase) activity. When BM enhancer of ALPase activity, was added to the primary osteoblast culture, B mRNA increased 6.9-fold after 24 h. In contrast, TGF-beta1 treatment, whi ALPase activity, rapidly and completely inhibited gene expression of BMP-

regulation of BMP-3 mRNA differed from that of BMP-3b, even though bo share 81% identity. These findings indicate that BMP-3b gene expression is osteoblastic differentiation and BMP-3b functions in highly differentiated o

PMID: 10079200 [PubMed - indexed for MEDLINE]

☐ **27:** Genome Res 1999 Feb;9(2):121-9 Related Articles, Nucleotide, Protein

Comment in:
- Genome Res. 1999 Feb;9(2):99-100

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Isolation of zebrafish gdf7 and comparative genetic mapping o belonging to the growth/differentiation factor 5, 6, 7 subgroup TGF-beta superfamily.

Davidson AJ, Postlethwait JH, Yan YL, Beier DR, van Doren C, Foern Celeste AJ, Crosier KE, Crosier PS.

Department of Molecular Medicine, School of Medicine, University of Auc Auckland, New Zealand.

The Growth/differentiation factor (Gdf) 5, 6, 7 genes form a closely related belonging to the TGF-beta superfamily. In zebrafish, there are three genes t the Gdf5, 6, 7 subgroup that have been named radar, dynamo, and contact. radar and dynamo both encode proteins most similar to mouse GDF6. The identity of these genes on the basis of amino acid similarities has not been have identified gdf7, a fourth zebrafish gene belonging to the Gdf5, 6, 7 sul assign correct orthologies and to investigate the evolutionary relationships mouse, and zebrafish Gdf5, 6, 7 subgroup, we have compared genetic map the zebrafish and mammalian genes. We have mapped zebrafish gdf7 to lin (LG) 17, contact to LG9, GDF6 to human chromosome (Hsa) 8 and GDF7 radar and dynamo genes have been localized previously to LG16 and LG19 A comparison of syntenies shared among human, mouse, and zebrafish gen indicates that gdf7 is the ortholog of mammalian GDF7/Gdf7. LG16 shares relationships with mouse chromosome (Mmu) 4, including Gdf6. Portions LG19 appear to be duplicate chromosomes, thus suggesting that radar and both orthologs of Gdf6. Finally, the mapping data is consistent with contact zebrafish ortholog of mammalian GDF5/Gdf5.

PMID: 10022976 [PubMed - indexed for MEDLINE]

☐ **28:** Development 1999 Mar;126(6):1305-15 Related Articles, Nucleotide, Protein

Full text article at dev.biologists.org

Mechanisms of GDF-5 action during skeletal development.

Francis-West PH, Abdelfattah A, Chen P, Allen C, Parish J, Ladher R, MacPherson S, Luyten FP, Archer CW.

Department of Craniofacial Development, Guy's, King's and St Thomas' Sc Dentistry, Guy's Tower, Floor 28, London Bridge, London, SE1 9RT, UK. pfrancis@hgmp.mrc.ac.uk

Mutations in GDF-5, a member of the TGF-beta superfamily, result in the a recessive syndromes brachypod (bp) in mice and Hunter-Thompson and Gr chondrodysplasias in humans. These syndromes are all characterised by the the appendicular skeleton and loss or abnormal development of some joints investigate how GDF-5 controls skeletogenesis, we overexpressed GDF-5 c limb development using the retrovirus, RCASBP. This resulted in up to a 3 in length of the skeletal elements, which was predominantly due to an incre number of chondrocytes. By injecting virus at different stages of developme that GDF-5 can increase both the size of the early cartilage condensation an developing skeletal element. Using in vitro micromass cultures as a model s study the early steps of chondrogenesis, we show that GDF-5 increases cho in a dose-dependent manner. We did not detect changes in proliferation. Ho suspension cultures showed that GDF-5 might act at these stages by increas adhesion, a critical determinant of early chondrogenesis. In contrast, pulse l experiments of GDF-5-infected limbs showed that at later stages of skeletal GDF-5 can increase proliferation of chondrocytes. Thus, here we show two of how GDF-5 may control different stages of skeletogenesis. Finally, our d levels of GDF-5 expression/activity are important in controlling the size of elements and provides a possible explanation for the variation in the severit defects resulting from mutations in GDF-5.

PMID: 10021348 [PubMed - indexed for MEDLINE]

☐ **29:** Invest Ophthalmol Vis Sci 1999 Feb;40(2):296-311 Relate

Bone morphogenetic proteins and growth and differentiation f the human cornea.

You L, Kruse FE, Pohl J, Volcker HE.

Department of Ophthalmology, University of Heidelberg Medical School, (

PURPOSE: To investigate transcription of members of the transforming gr (TGF)-beta superfamily and corresponding receptors in human corneal epitl stroma. METHODS: Transcription of bone morphogenetic proteins (BMP)- BMP-4, BMP-5, and BMP-7; growth- differentiation factor (GDF)-5), and receptors (BMPR) types I (BMPR-IA, BMPR-IB) and II (BMPR-II) was in reverse transcription-polymerase chain reaction (RT-PCR) in ex vivo and c For verification, PCR fragments were cloned and sequenced. DNA dot blot

performed to estimate the level of transcription. RNA dot blots were perfor determine expression of GDF-5. Expression of BMP receptor proteins was by immunohistochemistry. Single-cell clonal growth proliferation assays w using recombinant human GDF-5 and TGF-beta1. RESULTS: Transcriptio BMP-3, BMP-4, BMP-5, and BMP-7 and receptors of BMPR-IA, BMPR-II II was detected in ex vivo and cultured epithelium and stroma. The level of was higher in cultured stroma for all factors, but the level for the receptors cultured epithelium. In contrast GDF-5 was transcribed only in stromal cell that this cytokine may be an important mediator between keratocytes and ep Furthermore, GDF-5 inhibited proliferation of corneal epithelial and stroma CONCLUSIONS: Given the importance of the TGF-beta family during eml development, the results suggest that its members may be components of th cytokine network and may participate in the regulation of cellular proliferat differentiation.

PMID: 9950587 [PubMed - indexed for MEDLINE]

☐ **30:** Mech Dev 1998 Nov;78(1-2):135-40 Related Articles, Nucleotide, Protein

A novel growth differentiation factor-9 (GDF-9) related factor expressed with GDF-9 in mouse oocytes during folliculogenesis

Laitinen M, Vuojolainen K, Jaatinen R, Ketola I, Aaltonen J, Lehtonen Heikinheimo M, Ritvos O.

Department of Bacteriology and Immunology, Haartman Institute, P.O. Box University of Helsinki, FIN-00014, Helsinki, Finland. mplaitin@cc.helsink

Growth differentiation factor-9 (GDF-9) is a transforming growth factor-b (family member which is expressed in the oocytes in mouse ovaries (McGra Esquela, A.F., Lee, S.J., 1995. Oocyte-specific expression of growth/differe factor-9. Mol. Endocrinol. 9, 131-136). GDF-9 is indispensable for normal folliculogenesis since female mice deficient for the GDF-9 gene are infertil arrest of follicular growth at the primary follicle stage (Dong, J., Albertini, Nishimori, K., Kumar, T.R. , Lu, N., Matzuk, M.M., 1996. Growth differen 9 is required during early ovarian folliculogenesis. Nature 383, 531-535). W the GenBank Expressed Sequence Tag (EST) database with the mouse GDI sequence, and identified from a mouse 2-cell embryo library an EST cDNA a putative member of the TGF-b superfamily, and named it as GDF-9B. No hybridization analyses of mouse ovaries revealed a single transcript of appr kilobases (kb) for GDF-9B and of 2.0 kb for GDF-9. We cloned by reverse polymerase chain reaction from mouse ovarian RNA a partial 821-base pair cDNA that spans the sequence encoding the putative mature region of GDF COOH-terminal region of GDF-9B appears to be 53% homologous to GDF like GDF-9, GDF-9B lacks the cysteine residue needed for the covalent dim several TGF-b family members. Using in situ hybridization analysis, we de GDF-9B and GDF-9 mRNAs are co-localized in the oocyte. We also show and GDF-9 genes are co-ordinately expressed during follicular developmen

PMID: 9858711 [PubMed - indexed for MEDLINE]

☐ **31:** Arch Oral Biol 1998 Sep;43(9):745-51 Related Articles

Transforming growth factor-beta superfamily members expre incisor pulp.

Nakashima M, Toyono T, Murakami T, Akamine A.

Department of Operative Dentistry and Endodontology, Faculty of Dentistr University, Fukuoka, Japan.

The transforming growth factor (TGF)-beta superfamily comprises more th structurally related genes that have been implicated in embryonic induction morphogenesis. Different superfamily members may have distinct regulator tooth development and maintenance. Degenerate primer sets derived from t conserved carboxy terminal region of the TGF-beta superfamily were used transcriptase polymerase with poly(A)+ RNA from the rat incisor pulp as a TGF-beta superfamily members expressed in the pulp with known potential differentiate into odontoblasts and to form dentine were identified. Nucleoti analysis of the amplified cDNAs identified those encoding activin-betaB; b morphogenic protein (BMP)-2, -4, -7 and -8; growth/differentiation factor (and -6; and glial cell line-derived neurotrophic factor. In addition, Northern detected TGF-beta1 -beta2 and -beta3; activin-betaA; BMP-6 and GDF-7 m transcripts in the pulp. Coordinated expression of TGF-beta superfamily me pulp may be critical in tooth development and repair.

PMID: 9783830 [PubMed - indexed for MEDLINE]

☐ **32:** Growth Factors 1998;15(2):81-94 Relate

Characterization of growth factor responsiveness and alteratio growth factor homeostasis involved in the tumorigenic convers mouse oval cells.

Isfort RJ, Cody DB, Richards WG, Yoder BK, Wilkinson JE, Woychik

Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohi 8707, USA.

Five mouse oval cell lines were investigated in regards to their growth and factor (GDF) responsiveness and to changes in their GDF responsiveness fc tumorigenic conversion. In all 59 GDFs and 11 comitogens were evaluated responsiveness, depending on the mouse oval cell line under study, observe

oval cell GDF responsiveness during tumorigenic conversion revealed that variants displayed alterations in GDF responsiveness which correlated with tumorigenicity. In addition, analysis of autocrine/paracrine growth factor pr demonstrates that most tumorigenic variants produce growth factors. These demonstrate for the first time that (1) mouse oval cells respond to a wide va GDFs including various members of the interleukin, chemokine, stem cell f FGF, PDGF, TGF-beta, VEGF, insulin, CSF, TNF, HGF, and IFN growth a differentiation factor families in addition to multiple comitogens and (2) du tumorigenic conversion mouse oval cells undergo alterations which result i alterations in GDF responsiveness and the autocrine/paracrine production o GDFs.

PMID: 9505165 [PubMed - indexed for MEDLINE]

☐ **33:** Pharmazie 1998 Jan;53(1):51-7 Relate

Effects of growth factors on the proliferation of human keratir fibroblasts in vitro.

Kim DS, Korting HC, Schafer-Korting M.

Abteilung fur Pharmakologie und Toxikologie, Freie Universitat Berlin, Ge

Growth/differentiation factor-5 (GDF-5) is a new member of the transformi factor-beta (TGF-beta) superfamily of multifunctional peptide growth facto to mediate many key events in cell growth and development. The effects of other growth factors (epidermal growth factor, EGF; TGF-beta 1) on the pr human keratinocytes and fibroblasts compared with desoximetasone and ca have been investigated. The proliferation rate was determined by a hemocyt assay and the incorporation of [3H]-thymidine. Moreover, cell cycle analys performed and the influence on interleukin-1 alpha (IL-1 alpha) production keratinocytes was measured by enzyme-linked immunosorbent assay (ELIS its pronounced proinflammatory effect. In keratinocytes, GDF-5 stimulated proliferation to a minor extent. The drug already proved to be effective at v concentrations (0.1 ng/ml). Growth stimulatory effects with EGF have been only in keratinocyte basal medium (KBM), but not in keratinocyte growth n (KGM). TGF-beta 1 markedly inhibited the proliferation of keratinocytes at concentrations > 1 ng/ml. Calcipotriol and desoximetasone also showed a d dependent cell growth inhibition in epidermal cell cultures. IL-1 alpha synth greatly suppressed by calcipotriol 10(-8)-10(-6) M. EGF at 10 ng/ml, in con stimulated IL-1 alpha production. Neither GDF-5 nor TGF-beta 1 had a sig on IL-1 alpha production in keratinocyte monolayer cultures. In fibroblasts, induced very weak antiproliferative effects. Calcipotriol and desoximetason inhibited cell growth in fibroblast cultures whereas proliferation and DNA s were strongly stimulated by 1 ng/ml EGF. There was, however, a contradict TGF-beta 1 results on fibroblasts. Whereas TGF-beta 1 increased proliferat number determination and in the thymidine incorporation assay, MTT assay slight antiproliferative effects. Due to these controversial results, in additio

analysis was employed. TGF-beta 1 led to an increased S phase, which indi stimulation of cell division. The different results obtained with the MTT tes TGF-beta 1 may stimulate cell division of fibroblasts not only by increasing but also by shortening the G1 phase of the cell cycle.

PMID: 9476258 [PubMed - indexed for MEDLINE]

☐ **34:** J Cell Sci 1997 Dec;110 (Pt 24):3117-29 Related Articles

The combination of epidermal growth factor and transforming factor-beta induces novel phenotypic changes in mouse liver st lines.

Isfort RJ, Cody DB, Stuard SB, Randall CJ, Miller C, Ridder GM, Doe Richards WG, Yoder BK, Wilkinson JE, Woychik RP.

Proctor & Gamble Pharmaceuticals, Health Care Research Center, Mason, 9317, USA.

Mouse liver stem cell (oval cell) lines were investigated in order to determi which two families of growth and differentiation factors (GDFs), epidermal factor (EGF) family and transforming growth factor beta (TGF-beta) family regeneration. EGF family members, including EGF, amphiregulin, betacellu binding epidermal growth factor, and TGF-alpha, were mitogenic for oval c while TGF-beta family members, including TGF-beta1, TGF-beta2 and TG inhibited mitogenesis and induced apoptosis in oval cell lines. Surprisingly, combination of EGF family members and TGF-ss family members resulted proliferation nor apoptosis but instead in a novel cellular response, cellular tissue culture and morphological differentiation in Matrigel. Analysis of the transduction pathways activated by exposure of oval cell lines to either EGI beta, or TGF-beta indicated that novel combinations of intracellular signals following stimulation of the cells with the combination of EGF+TGF-beta. reveal that the dynamics of synergistic GDF action following tissue injury a regeneration results in a new level of complexity not obvious from the stud individual GDFs.

PMID: 9365282 [PubMed - indexed for MEDLINE]

☐ **35:** J Neurosci Res 1998 Jan 15;51(2):139-46 Related Articles

Bone morphogenetic proteins and their receptors: potential fu the brain.

Ebendal T, Bengtsson H, Soderstrom S.

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Ted.Ebendal@mun.uu.se

Transforming growth factors-beta (TGF-betas), activins, and bone morphog proteins (BMPs) comprise an evolutionarily well-conserved group of protei a number of cell differentiation, cell growth, and morphogentic processes d development. The superfamily of TGFbeta-related genes include over 25 m mammals several of which are expressed in the growing nervous system an important functions in regionalizing the early CNS. Cultured nerve cells sh responses to these factors. Recent developments have revealed that TGFbet and BMPs selectively signal to the responding cells via different hetero-olig complexes of type I and type II serine/threonine kinase receptors. The adult exhibits specific expression patterns of some of these receptors suggesting functions not only during development but also in the mature brain. In parti brain is expressing high levels of bone morphogenetic protein receptor type II), activin receptor type I (ActR-I), and activin receptor type IIA (ActR-II). indicates that osteogenic protein-1 (OP-1/BMP-7), BMP-2, and BMP-4 as activins may serve functions for brain neurons. Expression of the receptors overlaps in populations of neurons and has been shown to be regulated by b This suggests that brain neurons may use receptors BMPR-II and ActR-I to presence of BMPs. This may form a system parallel to the neurotrophin Trk kinase receptors regulating neuroplasticity and brain repair. The presence o brain is not well studied, but preliminary in situ data indicate that the BMP growth/differentiation factor (GDF)-1 and GDF-10 are distinctly but differe expressed at high levels in neurons expressing BMPR-II and ActR-I. The re mediating responses to these two GDFs remain, however, to be defined. Fir data show that the signal from the activated type I serine/threonine kinase r directly transduced to the nucleus by Smad proteins that become incorporat transcriptional complexes. Preliminary in situ hybridization observations de existence of different Smad mRNAs. It is concluded that BMPs and their si systems may comprise a novel pathway for control of neural activity and of pharmacological interventions rescuing brain neurons.

Publication Types:
- Review
- Review, tutorial

PMID: 9469567 [PubMed - indexed for MEDLINE]

☐ **36:** J Clin Invest 1997 Jul 15;100(2):321-30 Related Articles

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Ectopic induction of tendon and ligament in rats by growth an differentiation factors 5, 6, and 7, members of the TGF-beta ge

Wolfman NM, Hattersley G, Cox K, Celeste AJ, Nelson R, Yamaji N, D DiBlasio-Smith E, Nove J, Song JJ, Wozney JM, Rosen V.

Genetics Institute, Inc., Cambridge, Massachusetts 02140, USA.

Little is known about the regulatory signals involved in tendon and ligamen and this lack of understanding has hindered attempts to develop biologicall therapies for tendon and ligament repair. Here we report that growth and di factors (GDFs) 5, 6, and 7, members of the TGF-beta gene superfamily that related to the bone morphogenetic proteins, induce neotendon/ligament forr implanted at ectopic sites in vivo. Analysis of tissue induced by GDF-5, 6, containing implants by currently available morphological and molecular cri characterize tendon and ligament, adds further evidence to the idea that thes as signaling molecules during embryonic tendon/ligament formation. In adc comparative in situ localizations of the GDF-5, 6, and 7 mRNAs suggest th molecules are important regulatory components of synovial joint morphoge

PMID: 9218508 [PubMed - indexed for MEDLINE]

☐ **37:** Nature 1997 May 1;387(6628):83-90 Related Articles, Nucleotide, OMIM, Protein

Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member.

McPherron AC, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Johns Hopkins University Medicine, Baltimore, Maryland 21205, USA.

The transforming growth factor-beta (TGF-beta) superfamily encompasses of growth and differentiation factors playing important roles in regulating e development and in maintaining tissue homeostasis in adult animals. Using polymerase chain reaction, we have identified a new murine TGF-beta fami growth/differentiation factor-8 (GDF-8), which is expressed specifically in and adult skeletal muscle. During early stages of embryogenesis, GDF-8 ex restricted to the myotome compartment of developing somites. At later stag adult animals, GDF-8 is expressed in many different muscles throughout th determine the biological function of GDF-8, we disrupted the GDF-8 gene l targeting in mice. GDF-8 null animals are significantly larger than wild-typ show a large and widespread increase in skeletal muscle mass. Individual m mutant animals weigh 2-3 times more than those of wild-type animals, and in mass appears to result from a combination of muscle cell hyperplasia anc These results suggest that GDF-8 functions specifically as a negative regula muscle growth.

PMID: 9139826 [PubMed - indexed for MEDLINE]

☐ **38:** Kokubyo Gakkai Zasshi 1997 Mar;64(1):24-37 Relate

[Identification of receptors for bone morphogenetic proteins].

[Article in Japanese]

Nishitoh H.

Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry Medical and Dental University.

Bone morphogenetic protein (BMP)-7/osteogenic protein (OP)-1 and growth/differentiation factor (GDF)-5 are members of the BMP family. BM their effects through binding to two different types of serine/threonine kinas type I and type II. Here we investigated the binding and signaling properties 7/OP-1 and GDF-5 through type I and type II receptors. BMP-7/OP-1 was f Activin receptor-like kinase (ALK)-1 as well as ALK-3/BMPR-IA in ATDC When ALK-1 or ALK-3/BMPR-IA was stably transfected into mink lung ep ALK-1 and ALK-3/BMPR-IA mediated signals for BMP-7/OP-1 with hete signaling specificities. GDF-5 bound to ALK-6/BMPR-IB and BMP type II (BMPR-II) but not to ALK-3/BMPR-IA in ROB-C26 cells. Analysis using revealed that GDF-5 bound to ALK-6/BMPR-IB, but not to the other type I when expressed alone. When COS-1 cells were transfected with type II rece GDF-5 bound to Activin type II receptor (ActR-II) and type IIB receptors as BMPR-II but not to TGF-beta type II receptor. In the presence of type II rec 5 bound to different sets of type I receptors, but the binding was most effici 6/BMPR-IB compared to the other type I receptors. Moreover, GDF-5 trans signal efficiently by ALK-6/BMPR-IB in the presence of BMPR-II or ActR

PMID: 9125848 [PubMed - indexed for MEDLINE]

☐ **39:** Nat Genet 1996 Mar;12(3):315-7 Related Articles, OMIM

A human chondrodysplasia due to a mutation in a TGF-beta su member.

Thomas JT, Lin K, Nandedkar M, Camargo M, Cervenka J, Luyten FI

Bone Research Branch, National Institute of Dental Research, National Inst Health, Bethesda, Maryland 20892, USA.

The TGF-beta superfamily comprises a number of functionally diverse grov factors/signalling molecules (1) which elicit their response upon binding to threonine kinase receptors (2). We recently reported the isolation and chara two new members of the family, designated cartilage-derived morphogeneti (CDMP) 1 and 2 (ref. 3) which are closely related to the sub-family of bone morphogenetic proteins. CDMP-1 is predominantly expressed at sites of sk morphogenesis (3), and we now show that a mutation in hCDMP-1 is assoc recessive human chondrodysplasia (acromesomelic chondrodysplasia, Hunt

type (4,5)). The disorder, characterized by skeletal abnormalities restricted t
andlimb joints, is phenotypically similar to murine brachypodism (bp) whic
mutations in growth/differentiation factor-5 (Gdf-5) (6), the mouse homolo
hCDMP-1. Affected individuals are homozygous for a 22-bp (tandem-dupli
frameshift mutation in the mature region of CDMP-1. The resulting phenot
direct evidence for the involvement of CDMP-1 in human skeletal develop
represents the first human disorder attributable to a mutation in a TGF-beta
member.

PMID: 8589725 [PubMed - indexed for MEDLINE]

☐ **40:** Int J Dev Biol 1995 Dec;39(6):881-93 Relate

Divide, accumulate, differentiate: cell condensation in skeletal development revisited.

Hall BK, Miyake T.

Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canad

Cell condensation is a pivotal stage in skeletal development. Although prec
condensations normally exist for some 12 h, duration can vary. Variation is
between condensations for different cartilages (Meckel's vs. elastic ear carti
within a single condensation from which more than one skeletal element wi
the three components of the single first arch chondrogenic condensation. U
how duration of the condensation phase is established--how the condensatic
entered and exited during cell differentiation--remains a major area for futu
During chondrogenesis, cell-specific products such as collagen types II and
cartilage proteoglycan appear concomitant with condensation. Therefore, d
chondrogenesis, condensation precedes commitment of cells as prechondro
osteogenesis, however, differentiation of preosteoblasts precedes condensat
Therefore, during osteogenesis, condensation amplifies the number of comm
osteogenic cells. Further comparative analysis of skeletogenesis should pro
more rigorous understanding of cell commitment, when differentiation is in
commitment and differentiation are measured and the relationship of conde
onset of differentiation. Current knowledge of molecules characteristic of c
focused attention on extracellular matrix and cell surface components on th
and on growth factors homeobox genes and transcription factors on the oth
drawn together the molecular data for pre-chondrogenic condensations in di
form in Figure 2. Three major phases of chondrogenesis are identified: (a) e
mesenchymal interactions that precede condensation, (b) condensation itsel
differentiation. Although we label the third phase differentiation, it is impo
recognize that phases a and b also constitute aspects of chondroblast cell di
(see Dunlop and Hall, 1995 for a discussion of this point. The pre-condensa
characterized by expression of Hox genes, growth factors (TGF-beta and Bl
cell surface proteoglycan receptor, syndecan-1. Expression of Msx-1 and M
factors and syndecan continues into the condensation phase. Other molecul
versican, syndecan-3 and tenascin, present in low concentrations before con

are up-regulated during condensation. Yet other molecules--Hox genes, trar factors, growth factors (activin, BMP-4 and -5, GDF-5), cell adhesion mole proteoglycans--are only expressed during the condensation phase, while the factor Pax-1, fibronectin, hyaluronan and hyaladherin are expressed both du condensation. During condensation mRNAs for collagen types II and IX an protein of cartilage proteoglycan are up-regulated. Late in condensation and thereafter, the protein products of these genes accumulate as chondroblasts (see Fig. 2 for details). Not all the molecules present before, during of after can be placed into causal sequences. Some however can. In Figure 3 we sur causal sequences discussed in this paper as they relate to initiation of conde to transit from condensation to overt differentiation during chondrogenesis. Condensations form following activation of at least three pathways: (1) Init epithelial-mesenchymal interactions by tenascin, BMP-2, TGF beta-1 and N (2) Up-regulation of N-CAM by activin. (3) Up-regulation of fibronectin by further enhancing N-CAM accumulation (Fig. 3). It is by these three pathwa condensations are initiated and grow. Transition from condensation to overt differentiation is under both positive and negative control (Fig. 3). Syndeca fibronectin and so blocks N-CAM accumulation, preventing accumulation c cell

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